

HEALTH EFFECTS OF DEPLETED URANIUM IN EXPOSED GULF WAR VETERANS – A 12-YEAR FOLLOW-UP

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Background

- Friendly Fire incidents - inhalation exposure/wound contamination and embedded shrapnel
- Finding - relation between shrapnel status and elevated urinary uranium first observed in 1994 visit, confirmed in all 4 subsequent visits

Purpose of DU Surveillance Program

- Determine health effects, if any, in exposed population
- Develop methods to measure uranium exposure in novel exposure mode (embedded shrapnel)
- Examine surgical management of shrapnel



Summary of Surveillance Visits

<u>Year</u>	<u>Cases</u>	<u>Non-exposed</u>	<u>Total</u>
1993-4	33		33
1997	29	38	67
1999	21+29 new		50
2001	31+8 new (17 original cases)		39
2003	32		32

A total of 70 individuals involved in friendly fire incidents have been evaluated at Baltimore.

Surveillance Protocol

- Detailed questionnaire
- History
- Laboratory studies (blood/urine)
- Special studies

Surveillance Protocol Special Studies

- Semen analysis
- Genetox studies
- Neurocognitive battery

Demographic Characteristics for 2003 Cohort N=32

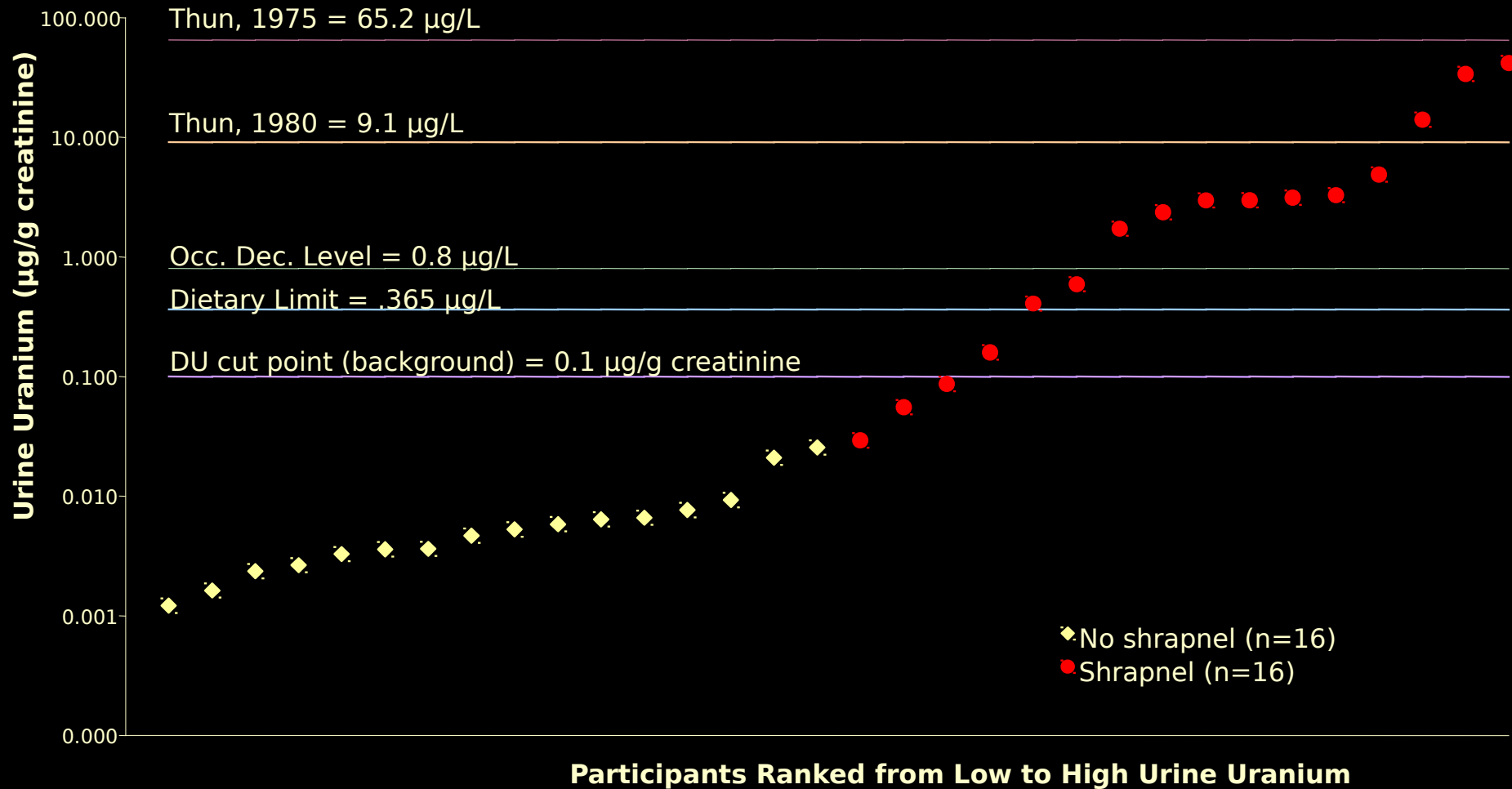
	N	% *
RACE		
African American	10	31
Caucasian	18	56
Hispanic	2	6
Other	2	6
EDUCATION		
9-12 years	6	19
Some college	21	66
College degree	3	9
Post college	2	6
MARITAL STATUS		
Never Married	4	13
Married	25	78
Divorced	3	9
AGE ^b		
	38.5 + 1.01	

* may not add to 100% due to rounding

^a At time of 2003 evaluation

^b Mean age at time of 2003 evaluation \pm SE, standard error of the mean)

Urine Uranium (2003) N=32



Clinical Findings

- No clinically significant differences detected between low and high uranium exposure groups
 - Hematology
 - Neuroendocrine
 - Chemistries
 - Neurocognitive

Renal Parameters (2003)

Laboratory test (normal range)	Low Uranium Group ^a (mean \pm SE(n))	High Uranium Group ^b (mean \pm SE(n))	T-test of Ranks
Serum glucose	100.68 \pm 4.12 (19)	94.85 \pm 2.16 (13)	0.63
Serum creatinine (0.0-1.4 mg/dL)	1.03 \pm 0.04 (19)	0.92 \pm 0.03 (13)	0.08
Serum uric acid (3.4-7 mg/dL)	5.77 \pm 0.25 (19)	5.56 \pm 0.45 (13)	0.34
Serum calcium (8.4-10.2 mg/dL)	9.28 \pm 0.09 (19)	9.25 \pm 0.07 (13)	0.85
Serum PO4 (2.7-4.5 mg/dL)	3.75 \pm 0.11 (19)	4.11 \pm 0.12 (13)	0.03

^a < 0.10 μ g/g creatinine

^b \geq 0.10 μ g/g creatinine

Renal Parameters (cont.)

Laboratory test (normal range)	Low Uranium Group ^a (mean \pm SE(n))	High Uranium Group ^b (mean \pm SE(n))	T-test of Ranks
Urine creatinine (1.3-2.6 g/24 hr)	1.82 \pm 0.15 (18)	1.98 \pm 0.15 (13)	0.31
Urine calcium (100-300 mg/24hr)	180.96 \pm 19.26 (18)	194.62 \pm 20.07 (12)	0.77
Urine PO ₄ (0.4-1.3 g/24hr)	0.92 \pm 0.10 (17)	1.04 \pm 0.15 (12)	0.46
Urine beta-2 microglobulin (0-160 μ g/g creatinine)	63.33 \pm 11.86 (12)	74.36 \pm 13.28 (11)	0.53
Urine intestinal alkaline phosphatase (IAP) U/g creatinine	0.36 \pm 0.08 (19)	0.37 \pm 0.14 (13)	0.84
Urine N-acetyl- β -D-glucosa-minidase (NAG) U/g creatinine	1.27 \pm 0.17 (19)	0.99 \pm 0.14 (13)	0.36
Urine total protein mg/g creatinine	147.48 \pm 12.66 (19)	202.67 \pm 31.02 (13)	0.10
Urine micro-albumin mg/L	20.64 \pm 10.91 (19)	6.92 \pm 3.15 (13)	0.31
Urine retinol binding protein mg/dL	0.11 \pm 0.07 (19)	0.06 \pm 0.05 (13)	0.58

^a < 0.10 μ g/g creatinine

^b \geq 0.10 μ g/g creatinine

Genotoxicity Parameters (2003)

Laboratory test	Low Uranium Group^a (mean\pmSE(n))	High Uranium Group^a (mean\pmSE(n))	Mann- Whitney Test (p)
SCE ^c untreated	4.77 \pm 0.30 (16)	4.75 \pm 0.35 (10)	0.812
CA, untreated	0.00 \pm 0.00 (19)	0.01 \pm 0.01 (13)	0.227
HPRT MF ^e	15.91 \pm 1.96 (19)	32.38 \pm 13.75 (13)	0.803

^a < 0.10 μ g/g creatinine

^b \geq 0.10 μ g/g creatinine

^c SCE, mean sister chromatid exchanges per cell

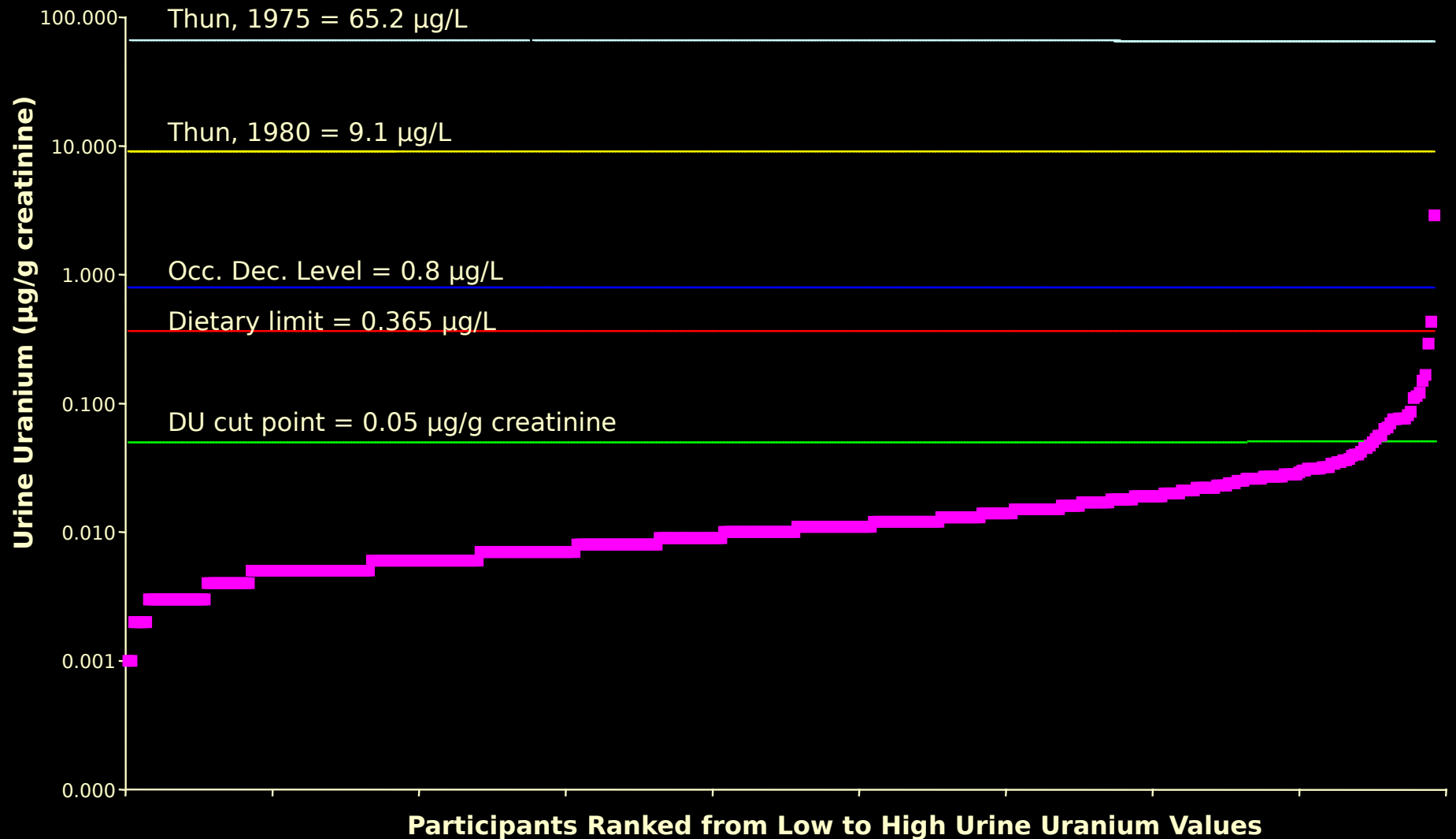
^d CA, mean chromosomal aberrations per cell

^e HPRT MF, hypoxanthine phosphoribosyl transferase mutation frequency

Radiation Dose Estimate from Whole Body Counting

- Nine veterans with whole body measurements above background
- Radiation dose estimates calculated using ICRP 30 Biokinetic model for U
 - 0.01 to 0.11 rem/year
 - 0.61 to 5.33 rem/50 years
- Public dose limit: 0.1 rem/year
- Occupational limit: 5 rem/year

Urine Uranium in GWI Mailed-in Samples N=446



DU Exposure Assessment in U.S. Soldiers: Accurate Analysis of U^{235} / U^{238} Isotopic Ratios

- **Goal**

- To develop an analytical technique(s) capable of accurately detecting the presence of DU in urine samples with U concentrations in the normal range

- **Purpose**

- To identify low level exposure to DU in soldiers with potential exposure by inhalation, ingestion, wound contamination and/or shrapnel.

Collaborators

Armed Forces Institute of Pathology (AFIP)

John Ejnick, PhD

Todor Todorov, PhD

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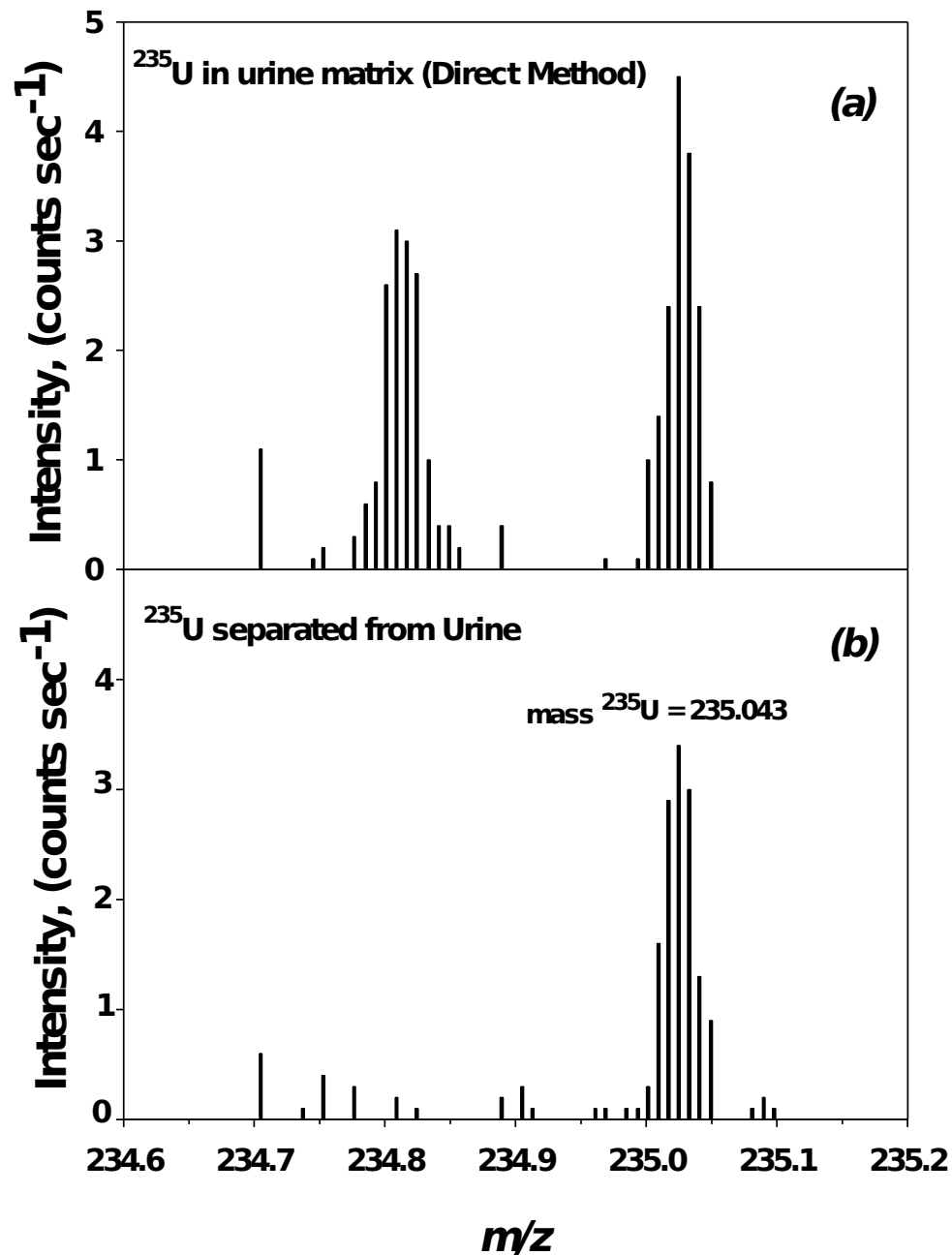
Ge Xiao, PhD

Methods Development

- ThermoFinnigan Element 1 magnetic sector inductively coupled plasma-mass spectrometer in low resolution (~ 300) (ICP-MS-TFE1) (UCSC)
- ICP-MS Elan 6100 Dynamic Reaction Cell (ICP-MS-DRC1) (AFIP)

ICP/MS Total Uranium and Isotopic Analysis of Mail-In Urine Samples (Gulf War Vets)

	Uranium Concentration mcg/L	Isotopic Analysis U235/U238
P001	0.334	0.0076
P002	0.075	0.0088 ←
P003	0.131	0.0078
P004	0.129	0.0075
P005	0.131	<u>0.0027</u>
P006	0.115	0.0076
P007	0.077	0.0091 ←
P008	0.024	0.0116 ←

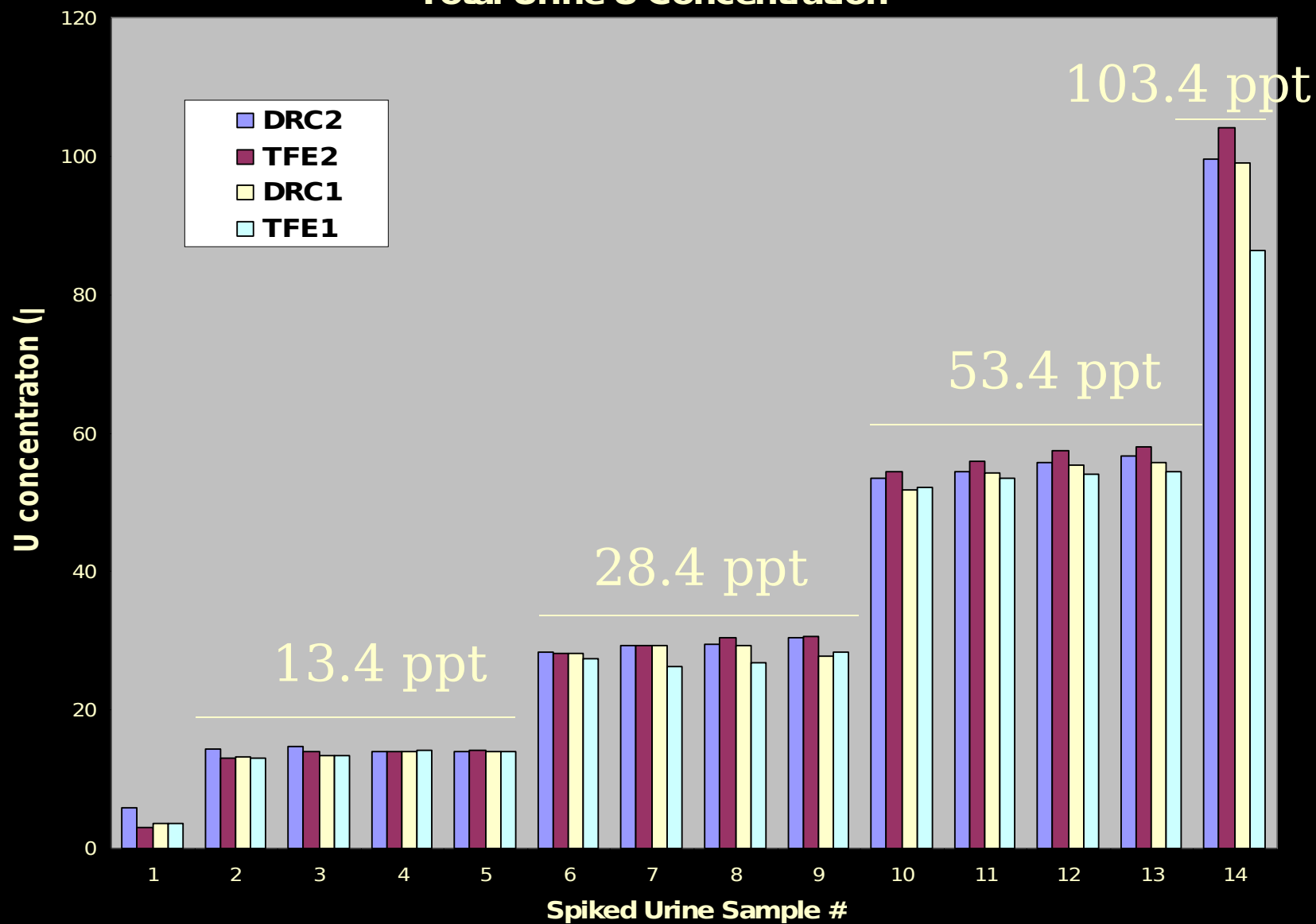


Inter-Laboratory QA/QC Study Samples

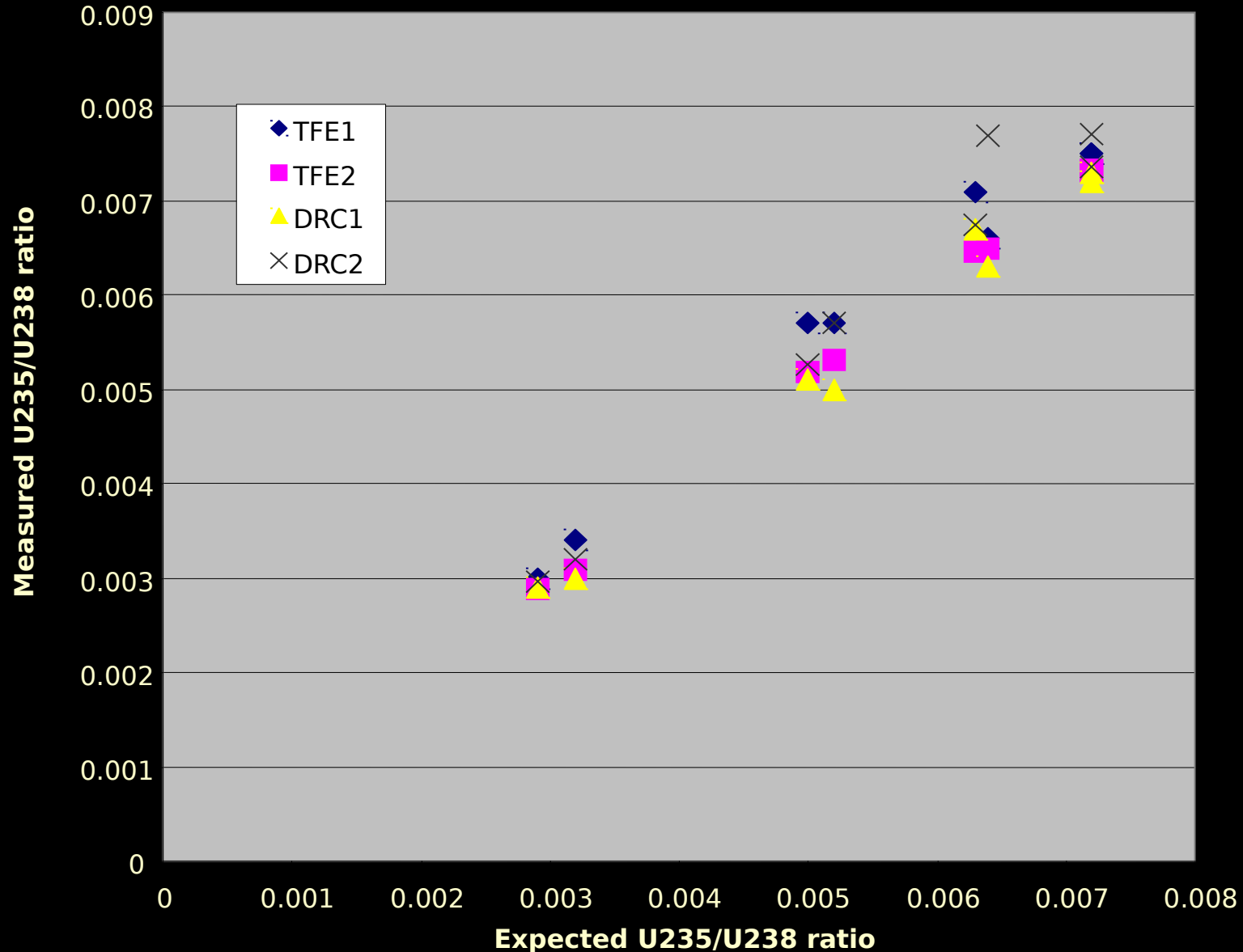
- Urine specimen spiked with U
 - U Concentrations (6): 13 ppt to 10,000 ppt
 - % U²³⁵: 0.26, 0.38, 0.55, 0.65, 0.72
- Twenty-two (22) unknowns: Selected from DU Follow-Up Program specimens
 - U Concentration range: 3.9 ppt to 4,500 ppt

Spiked Urine Samples QA/QC Study

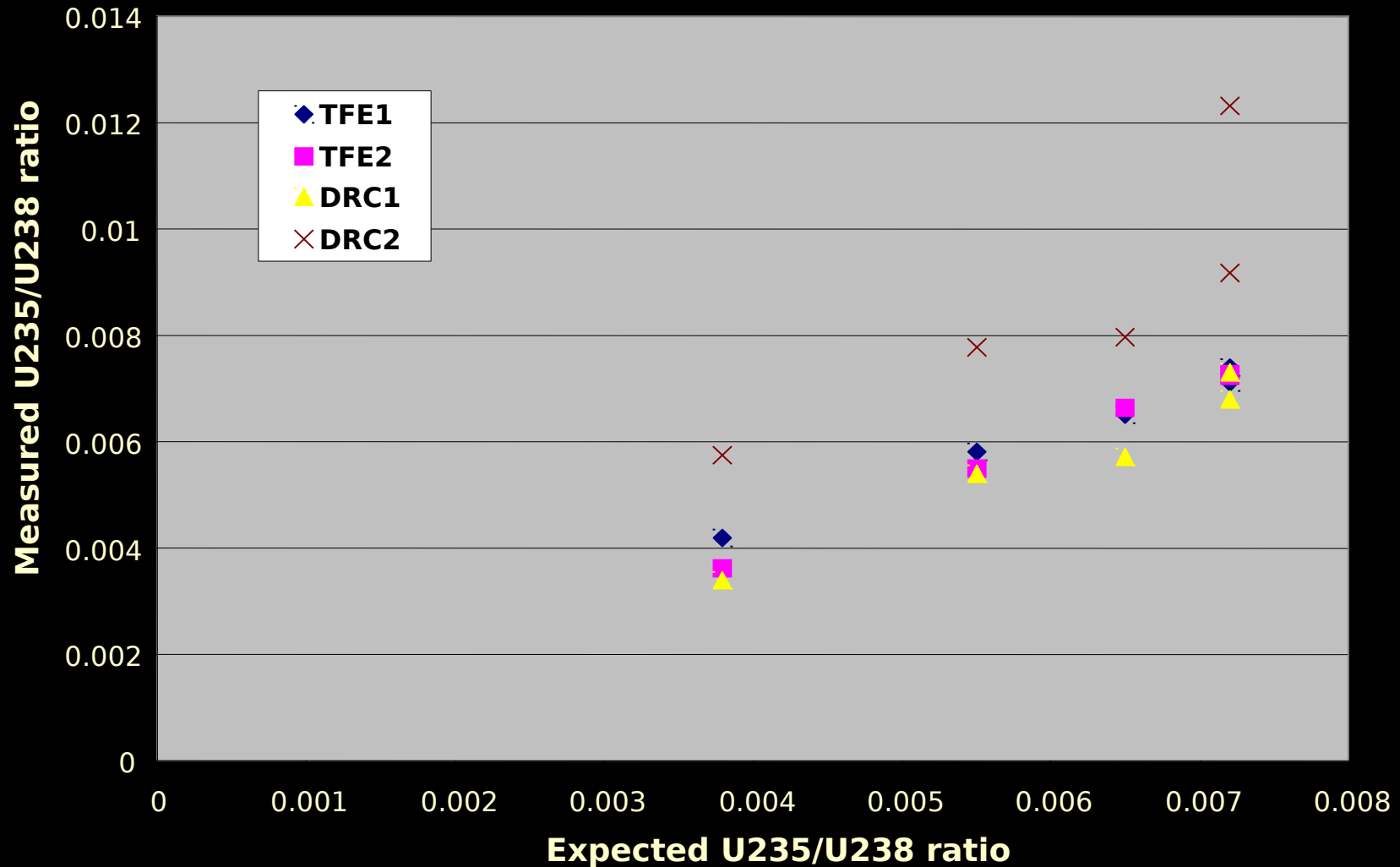
Total Urine U Concentration



Isotopic Ratio Spiked Samples [U] 28 and 53 pptr



Isotopic Ratio Spiked Samples [U] < 15 pptr



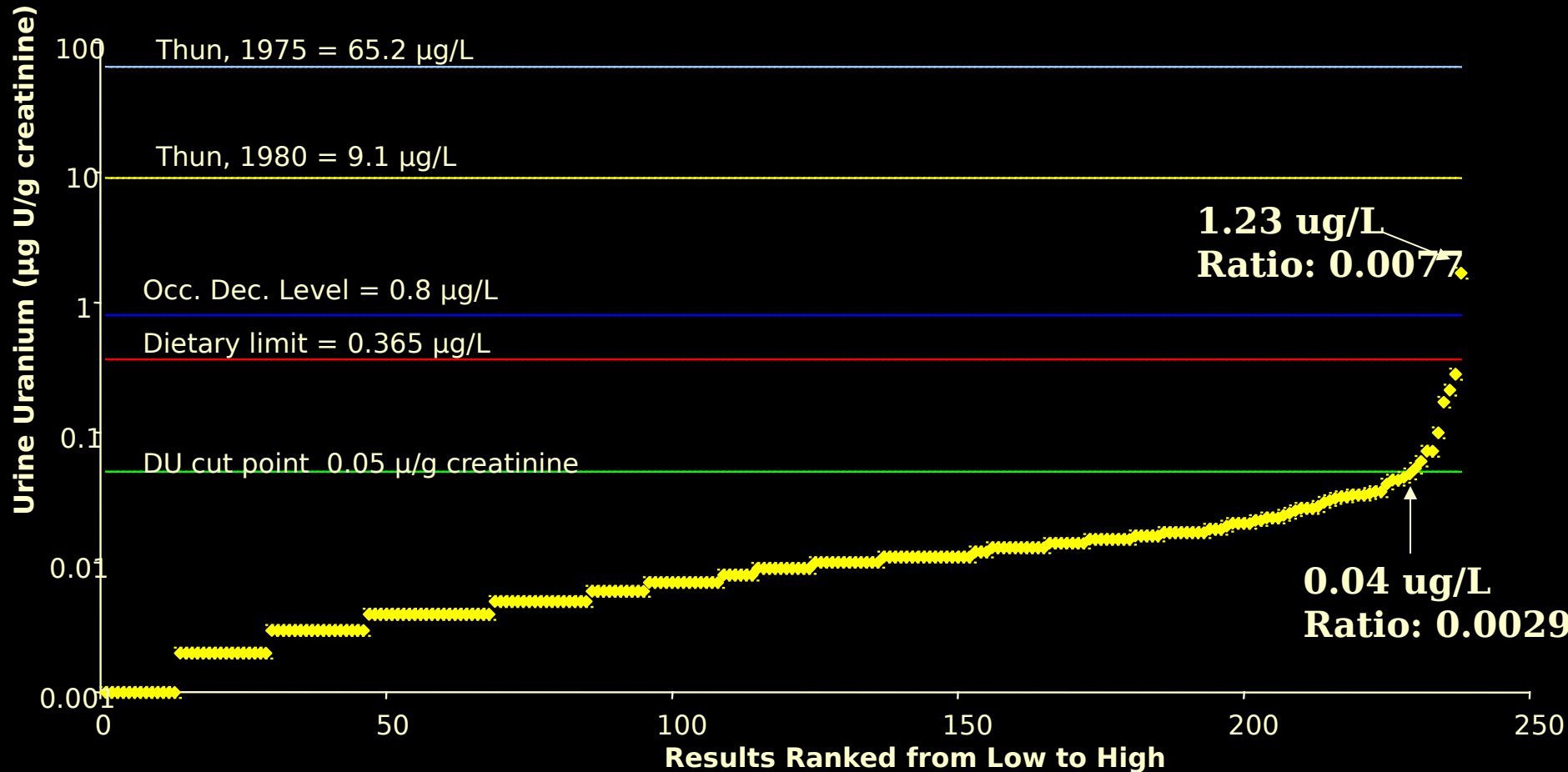
DRC1

Urine Uranium Isotopic Analysis

- **ICP Elan 6100 Dynamic Reaction Cell MS**
- **DRC eliminates interference (polyatomic)**
- **Acidification with Optima grade concentrated Nitric acid to 2% nitric**
- **Urine samples > 100 ppt analyzed directly**
- **Urine samples < 100 ppt dry ashed**
- **Internal standard: ^{233}U**
- **Detection limit for U quantitation: 0.1 ppt**
- **Detection limit for isotopic analysis: 10 ppt**

Urine Uranium Results from OIF

N=238



Current Protocol for DU Urine Testing and Referral to VA Follow-Up Program

If:

- [total U] is < 50 ng/g cre **and** negative for DU:
No follow-up necessary
- [total U] is < 50 ng/g cre **and** positive for DU:
Repeat urine test in 6 months
- [total U] is > 50 ng/g cre **or** positive for DU:
Repeat urine test now
- Repeat [total U] is still > 50 ng/g cre **or** positive for DU: Conduct skeletal survey for evidence of embedded fragments
- [total U] > 50 ng/g cre **and** positive for DU w/ evidence of shrapnel:
Referral to VA In-Patient DU Follow-Up Program

Depleted Uranium Follow-Up Program Collaborators

- Melissa McDiarmid, MD, MPH
- Katherine Squibb, PhD
- Susan Engelhardt, RN, MN
- Marc Oliver, RN, MPH
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- Bruce Kaup, MD
- Lawrence Brown, MD
- David Jacobson-Kram, PhD
- P. David Wilson, PhD